UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/622,076	07/17/2003	Rudolf Gilmanshin	C0989.70054US00	1842

7590 11/28/2007

Helen C. Lockhart
Wolf, Greenfield & Sacks, P.C.
Federal Reserve Plaza
600 Atlantic Avenue
Boston, MA 02210

EXAMINER	
BERTAGNA, ANGELA MARIE	

ART UNIT	PAPER NUMBER
1637	

MAIL DATE	DELIVERY MODE
11/28/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/622,076	GILMANSHIN, RUDOLF
	Examiner	**Art Unit**
	Angela Bertagna	1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-7,9,11-17,19-34,68,91 and 125-130* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-7,9,11-17,19-34,68,91 and 125-130* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/5/07*.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 10, 2007 has been entered. Claims 1, 2, 5-7, 9, 11-17, 19-34, 68, 91, and 125-130 are currently pending and will be examined on the merits.

Information Disclosure Statement

2. Applicant's submission of an Information Disclosure Statement on November 5, 2007 is acknowledged. A signed copy is enclosed.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1, 2, 5-7, 11, 14, 16, 24-26, 31, 91, and 126-129 are rejected under 35 U.S.C. 102(b) as being anticipated by Cheng et al. (Biochemical and Biophysical Research Communications (1991) 174(2): 785-789; newly cited).

These claims are drawn to a method for analyzing a nucleic acid polymer. The method comprises contacting the nucleic acid polymer with a conjugate comprising a nucleic acid binding enzyme and a nucleic acid tag molecule that are covalently linked to each another. The nucleic acid binding enzyme binds non-specifically to the nucleic acid polymer, and the nucleic acid tag molecule binds specifically to the nucleic acid polymer. A pattern of the binding between the conjugate and the nucleic acid polymer is then determined. This determination is not based on the catalytic activity of the nucleic acid binding enzyme.

Cheng analyzed the binding between HIV-1 reverse transcriptase and a primed nucleic acid template using UV crosslinking (see abstract and pages 786-787).

Regarding claims 1, 2, 91, and 126-129, Cheng teaches a method for analyzing a nucleic acid polymer (see page 786, last paragraph – page 787, first paragraph). Here, Cheng teaches combining a nucleic acid polymer (rA_{12-18}) with a nucleic acid tag molecule (dT_{10}) and a nucleic acid binding enzyme (HIV-1 reverse transcriptase) and performing UV crosslinking. The UV crosslinking step produces a covalently bound conjugate comprising the nucleic acid tag molecule and the nucleic acid binding enzyme that is contacted with the nucleic acid polymer. When the reactants are combined in solution (page 786, last paragraph), the HIV-1 RT inherently binds the nucleic acid molecule non-specifically and translocates along the polymer. Since the nucleic acid tag molecule (dT_{10}) is complementary to the nucleic acid polymer (rA_{12-18}), it binds in a sequence-specific manner to label the nucleic acid polymer. In the method of Cheng, the reverse transcriptase enzyme does not cleave the nucleic acid polymer. The analysis of the crosslinked complexes by electrophoresis (Figures 1 & 2) constitutes determining a binding pattern of the conjugate to the nucleic acid polymer. This determination is based on the

detection of radioactive labels present on the nucleic acid polymer and the nucleic acid binding enzyme, and therefore, is not dependent on the catalytic activity of HIV-1 RT (see pages 786-787 and Figures 1-2). Finally, the HIV-1 RT taught by Cheng is a nuclease since it inherently possesses RNase H activity (page 785, 1st paragraph). Therefore, Cheng anticipates the methods of claims 1, 2, 91, and 126-129.

Regarding claims 5-7 and 11, Cheng teaches that the nucleic acid polymer is RNA, the nucleic acid tag molecule is a DNA, and the enzyme is a DNA polymerase (page 786, last paragraph). Also, the nucleic acid tag molecule taught by Cheng is 10 nucleotides in length (page 786, last paragraph), which is within the claimed length range of 5-50 nucleotides.

Regarding claims 14, 16, and 31, Cheng teaches that the nucleic acid binding enzyme and the nucleic acid polymer are labeled with detectable moieties, specifically radioactive labels (page 786, last paragraph). Cheng also teaches indirect detection of the nucleic acid binding enzyme by measuring the signal from the polymer in combination with the signal from a radiolabeled nucleotide substrate (dTTP) bound to the enzyme (pages 786-788 and Figures 1-2).

Regarding claims 24-26, the nucleic acid polymer taught by Cheng is neither an in vitro amplified nucleic acid nor an antisense molecule (page 786). Also, the nucleic acid molecule taught by Cheng (dT_{10}) does not hybridize to bacterial or viral-specific sequences.

5. Claim 125 is rejected under 35 U.S.C. 102(b) as being anticipated by Fisher et al. (US 6,362,328 B1; cited previously) as evidenced by Chaudhry et al. (Nucleic Acids Research (1995) 23(19): 3805-3809; newly cited).

Claim 125 is drawn to a method for analyzing a nucleic acid polymer. The method comprises contacting the nucleic acid polymer with a conjugate comprising a nucleic acid tag molecule covalently linked to a DNA repair enzyme, a helicase, or a ligase. The nucleic acid binding enzyme binds non-specifically to the nucleic acid polymer, and the nucleic acid tag molecule binds specifically to the nucleic acid polymer. A pattern of the binding between the conjugate and the nucleic acid polymer is then determined.

Fisher teaches a method for analyzing a nucleic acid polymer (such as DNA or RNA) using a conjugate consisting of a covalently linked oligonucleotide and nuclease P1 (see abstract and column 4, lines 36-64). The nucleic acid tag oligonucleotide hybridizes specifically to the nucleic acid target (column 6, lines 5-12), and the nucleic acid binding enzyme (nuclease P1) associates non-specifically with the nucleic acid polymer. After specific hybridization of the oligonucleotide tag molecule to the nucleic acid polymer, the hybridization pattern was detected (column 4, lines 53-64). Finally, as evidenced by Chaudhry et al., the S1 and P1 nucleases used in the conjugates of Fisher are DNA repair enzymes (see pages 3806-3808 and Figures 1-4).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1, 2, 5-7, 9, 11-15, 21-28, 30, 31, 91, and 126-130 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fisher et al. (US 6,362,328 B1; cited previously) as evidenced by Chaudhry et al. (Nucleic Acids Research (1995) 23(19): 3805-3809; newly cited) in view of Kigawa et al. (US 5,965,361; cited previously).

These claims are drawn to a method for analyzing a nucleic acid polymer. The method comprises contacting the nucleic acid polymer with a conjugate comprising a nucleic acid binding enzyme and a nucleic acid tag molecule that are covalently linked to each other. The nucleic acid binding enzyme binds non-specifically to the nucleic acid polymer, and the nucleic acid tag molecule binds specifically to the nucleic acid polymer. A pattern of the binding between the conjugate and the nucleic acid polymer is then determined. This determination is not based on the catalytic activity of the nucleic acid binding enzyme.

Regarding claims 1, 2, 91, and 126-130, Fisher teaches a method for analyzing a nucleic acid polymer comprising

(a) contacting the nucleic acid polymer with a conjugate comprising a nucleic acid tag molecule and a nucleic acid binding enzyme that are covalently linked to each other (column 4, lines 37-53)

(b) allowing the nucleic acid binding enzyme to bind to the nucleic acid polymer non-specifically and translocate along the polymer (column 4, lines 37-53)

(c) allowing the nucleic acid tag molecule to bind to the nucleic acid polymer in a sequence-specific manner, thereby labeling the nucleic acid polymer (see column 4, lines 37-53 column 6, lines 5-23 teach that the tag molecule binds in a sequence-specific fashion)

(d) determining a pattern of binding of the conjugate to the nucleic acid polymer (column 4, lines 46-64).

Further regarding claims 1, 91, and 126-130, Fisher teaches that the nucleic acid binding enzyme binds to the nucleic acid polymer without cleavage (column 2, lines 48-61).

Regarding claims 5, 6, and 11, Fisher teaches that the nucleic acid polymer is DNA (column 8, lines 15-43), the nucleic acid tag molecule is DNA or RNA (column 4, lines 39-40), and the nucleic acid binding enzyme is a nuclease or DNA repair enzyme (column 2, lines 48-61 and column 4, lines 37-39). As evidenced by Chaudhry et al., the S1 and P1 enzymes used in the conjugates of Fisher are DNA repair enzymes (see pages 3806-3808 and Figures 1-4).

Regarding claim 7, Fisher teaches a nucleic acid tag sequence of 35 nucleotides (column 6, lines 15-16), which is within the claimed length range of 5-50 nucleotides.

Regarding claim 9, Fisher teaches that the nucleic acid tag molecule and the nucleic acid binding enzyme are conjugated using a linker molecule (column 4, lines 40-45).

Regarding claim 12, Fisher teaches that the pH of the reaction is maintained above pH 7.0, thereby preventing P1 nuclease-catalyzed cleavage of the nucleic acid substrate (column 2, lines 48-54).

Regarding claims 24 and 25, the plasmid DNA target used in the Fisher method was not amplified in vitro prior to hybridization, nor were the oligonucleotide probes designed to function as antisense molecules (Example 11, column 8, lines 15-43).

Regarding claim 26, Fisher teaches probes specific for eukaryotic sequences (column 6, lines 5-12).

Regarding claims 27, 28, and 30, the P1 nuclease and oligonucleotide components of the conjugate taught by Fisher are covalently linked (column 4, lines 37-39). Therefore, the nucleic acid tag molecule is "labeled with an agent", specifically the P1 nuclease. Furthermore, although the pH of the reaction has been adjusted to prevent P1 nuclease from cleaving the nucleic acid substrate (column 2, lines 48-54), the enzyme has not been otherwise modified (i.e. by mutation), and therefore, is still inherently capable of cleaving (i.e. modifying) a nucleic acid molecule.

Regarding claim 31, Fisher teaches detection of the hybridization products using chemiluminescence (column 4, lines 53-64). This method indirectly detects the presence of the binding agent (P1 nuclease).

Fisher teaches detecting the binding of the oligonucleotide-nuclease conjugate to the nucleic acid polymer using a chemiluminescent assay that depends on the catalytic activity of the nuclease rather a method that does not depend on the catalytic activity of the nuclease as required by claims 1, 91, and 126-129. This method is based on detection of the nucleic acid binding enzyme rather than the nucleic acid tag molecule as required by claim 130. Fisher also does not teach labeling the nucleic acid tag molecule and the nucleic acid binding enzyme with detectable moieties, such as fluorophores, to permit fluorescence in situ hybridization as required by claims 13-15 and 21-23.

Kigawa teaches methods of analyzing nucleic acids using a conjugate comprising an oligonucleotide probe and RecA (see abstract and column 4, lines 7-31).

Regarding claims 1, 2, 91, and 125-130, the method of Kigawa comprises

(a) contacting the nucleic acid polymer with a conjugate comprising a nucleic acid tag molecule and a nucleic acid binding enzyme (see column 4, lines 7-25 or column 17, lines 5-25,

where a conjugate comprising a biotinylated nucleic acid molecule (the "nucleic acid tag molecule") and Cy3-labeled RecA (the nucleic acid binding enzyme) is added to a target nucleic acid; column 16, lines 5-45 teach preparation of the nucleic acid probe/Rec A conjugate)

(b) allowing the nucleic acid binding enzyme to bind to the nucleic acid polymer non-specifically and translocate along the polymer without cleavage of the polymer (column 2, lines 39-44 and column 17, lines 5-25)

(c) allowing the nucleic acid tag molecule to bind to the nucleic acid polymer in a sequence-specific manner, thereby labeling the nucleic acid polymer (see column 17, lines 5-25; see also column 4, lines 16-18 and column 6, lines 11-15)

(d) determining a pattern of binding of the conjugate to the nucleic acid polymer (column 17, lines 59-67; see also column 4, lines 27-31).

Further regarding claims 1, 91, and 126-130, Kigawa teaches that the binding of the conjugate to the nucleic acid polymer is determined by measuring the fluorescence of a Cy3 label attached to the RecA protein or the signal of FITC derived from the biotinylated nucleic acid tag molecule (see column 17, lines 59-67). These methods do not rely on the catalytic activity of the nucleic acid binding enzyme. Also, when the binding pattern is determined using a signal derived from the biotinylated nucleic acid tag molecule (column 17, lines 59-67), the nucleic acid tag molecule is detected.

Regarding claims 5 and 6, Kigawa teaches that the nucleic acid polymer and nucleic acid tag molecule are DNA molecules (column 4, lines 47-49 and column 5, lines 57-59).

Regarding claim 11, Kigawa teaches that the enzyme is a DNA repair enzyme (see abstract, where RecA is taught).

Regarding claims 13-15 and 27, Kigawa teaches that the nucleic acid tag molecule is labeled with a first detectable moiety (or agent) and the nucleic acid binding enzyme is labeled with a second detectable moiety (see Example 3, column 17, lines 59-67, where Kigawa teaches that RecA is labeled with the Cy3 fluorophore and the nucleic acid tag molecule is labeled with biotin; see also column 6, lines 22-32, where Kigawa teaches labeling of the nucleic acid tag and RecA).

Regarding claim 21, Kigawa teaches detection using FISH (see Example 3, column 17, lines 59-67).

Regarding claims 22 and 23, Kigawa teaches that the detectable moiety is a fluorescent molecule and that detection proceeds using a fluorescence detection system (column 6, lines 22-25; see also column 17, lines 59-67, where FITC fluorescence derived from the biotinylated nucleic acid tag molecule is detected using a fluorescence microscope).

Regarding claims 24-26, Kigawa teaches examples of nucleic acid tag molecules that are not in vitro amplified nucleic acids (see column 16, lines 5-18; see also column 5, line 57 – column 6, line 10). Kigawa also does not teach that the nucleic acid tag molecules are antisense molecules. Finally, the probe taught by Kigawa in Example 3 is specific for a human chromosome 1 satellite III sequence (column 16, lines 5-7). This is not a bacterial or viral-specific probe.

Regarding claim 31, Kigawa teaches that the nucleic acid binding enzyme is detected indirectly, specifically by binding of an antibody specific to the enzyme (column 3, line 64 – column 4, line 5 and column 6, lines 27-32).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Kigawa to the method taught by Fisher. An ordinary artisan would have been motivated to label the nucleic acid tag molecule and/or the nucleic acid binding enzyme with detectable moieties, such as fluorophores, recognizing that these labels permitted direct detection of the bound enzyme-oligonucleotide conjugate. An ordinary artisan would have recognized that direct detection using a fluorescent label was faster and simpler than the indirect methods relying on nuclease activity taught by Fisher. An ordinary artisan would also have been motivated to detect the bound oligonucleotide-enzyme conjugate using any detection method taught by Kigawa, including direct detection using fluorescent, chemiluminescent, or radioactive labels bound to the oligonucleotide tag molecule or the nucleic acid binding enzyme or indirect detection based on biotin and a labeled avidin molecule, recognizing that these detection methods were art-recognized equivalents useful for the same purpose. As noted in MPEP 2144.06, substitution of art-recognized equivalents is prima facie obvious. Since the methods of Fisher and Kigawa were directed to the same problem, namely detection of target nucleic acids using enzyme-labeled oligonucleotides, an ordinary artisan would have had a reasonable expectation of success in substituting the direct and indirect detection methods taught by Kigawa for the indirect detection methods taught by Fisher. An ordinary artisan also would have had a reasonable expectation of success in labeling nucleic acid tag molecule and/or nuclease P1 component(s) of the conjugate taught by Fisher, as suggested by Kigawa, since methods for labeling proteins and nucleic acids with fluorescent, chemiluminescent, hapten, or radioactive labels were well known in the art as evidenced by the teachings of Kigawa (column 6, line 22 –

column 7, line 60). Thus, the methods of claims 1, 2, 5-7, 9, 11-15, 21-28, 30, 31, 91, and 126-130 are prima facie obvious over Fisher as evidenced by Chaudhry in view of Kigawa.

8. Claims 1, 2, 5-7, 9, 11-13, 16, 17, 22-31, 91, and 126-130 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fisher et al. (US 6,362,328 B1; cited previously) as evidenced by Chaudhry et al. (Nucleic Acids Research (1995) 23(19): 3805-3809; newly cited) in view of Rye et al. (Nucleic Acids Research (1992) 20(11): 2803-2812; newly cited) and further in view of Thompson et al. (US 6,348,317 B1; newly cited).

These claims are drawn to a method for analyzing a nucleic acid polymer. The method comprises contacting the nucleic acid polymer with a conjugate comprising a nucleic acid binding enzyme and a nucleic acid tag molecule that are covalently linked to each another. The nucleic acid binding enzyme binds non-specifically to the nucleic acid polymer, and the nucleic acid tag molecule binds specifically to the nucleic acid polymer. A pattern of the binding between the conjugate and the nucleic acid polymer is then determined using a backbone-specific label on the nucleic acid polymer. This determination is not based on the catalytic activity of the nucleic acid binding enzyme.

Regarding claims 1, 2, 91, and 126-130, Fisher teaches a method for analyzing a nucleic acid polymer comprising

(a) contacting the nucleic acid polymer with a conjugate comprising a nucleic acid tag molecule and a nucleic acid binding enzyme that are covalently linked to each other (column 4, lines 37-53)

(b) allowing the nucleic acid binding enzyme to bind to the nucleic acid polymer non-specifically and translocate along the polymer (column 4, lines 37-53)

(c) allowing the nucleic acid tag molecule to bind to the nucleic acid polymer in a sequence-specific manner, thereby labeling the nucleic acid polymer (see column 4, lines 37-53 column 6, lines 5-23 teach that the tag molecule binds in a sequence-specific fashion)

(d) determining a pattern of binding of the conjugate to the nucleic acid polymer (column 4, lines 46-64).

Further regarding claims 1, 91, and 126-130, Fisher teaches that the nucleic acid binding enzyme binds to the nucleic acid polymer without cleavage (column 2, lines 48-61).

Regarding claims 5, 6, and 11, Fisher teaches that the nucleic acid polymer is DNA (column 8, lines 15-43), the nucleic acid tag molecule is DNA or RNA (column 4, lines 39-40), and the nucleic acid binding enzyme is a nuclease or DNA repair enzyme (column 2, lines 48-61 and column 4, lines 37-39). As evidenced by Chaudhry et al., the S1 and P1 enzymes used in the conjugates of Fisher are DNA repair enzymes (see pages 3806-3808 and Figures 1-4).

Regarding claim 7, Fisher teaches a nucleic acid tag sequence of 35 nucleotides (column 6, lines 15-16), which is within the claimed length range of 5-50 nucleotides.

Regarding claim 9, Fisher teaches that the nucleic acid tag molecule and the nucleic acid binding enzyme are conjugated using a linker molecule (column 4, lines 40-45).

Regarding claim 12, Fisher teaches that the pH of the reaction is maintained above pH 7.0, thereby preventing P1 nuclease-catalyzed cleavage of the nucleic acid substrate (column 2, lines 48-54).

Regarding claims 24 and 25, the plasmid DNA target used in the Fisher method was not amplified in vitro prior to hybridization, nor were the oligonucleotide probes designed to function as antisense molecules (Example 11, column 8, lines 15-43).

Regarding claim 26, Fisher teaches probes specific for eukaryotic sequences (column 6, lines 5-12).

Regarding claims 27, 28, and 30, the P1 nuclease and oligonucleotide components of the conjugate taught by Fisher are covalently linked (column 4, lines 37-39). Therefore, the nucleic acid tag molecule is "labeled with an agent", specifically the P1 nuclease. Furthermore, although the pH of the reaction has been adjusted to prevent P1 nuclease from cleaving the nucleic acid substrate (column 2, lines 48-54), the enzyme has not been otherwise modified (i.e. by mutation), and therefore, is still inherently capable of cleaving (i.e. modifying) a nucleic acid molecule.

Regarding claim 31, Fisher teaches detection of the hybridization products using chemiluminescence (column 4, lines 53-64). This method indirectly detects the presence of the binding agent (P1 nuclease).

Fisher teaches detecting the binding of the oligonucleotide-nuclease conjugate to the nucleic acid polymer using a chemiluminescent assay that depends on the catalytic activity of the nuclease rather a method that does not depend on the catalytic activity of the nuclease as required by claims 1, 91, and 126-129. This method is based on detection of the nucleic acid binding enzyme rather than the nucleic acid tag molecule as required by claim 130. Fisher also does not teach labeling the nucleic acid polymer with a backbone specific label as required by claims 16 and 17. Finally, Fisher does not teach labeling the nucleic acid tag molecule with a fluorophore or a photocleaving agent as required by claims 13, 22, 23, and 29.

Rye teaches a method for detecting nucleic acid hybridization reactions using fluorescent intercalators that show strong fluorescent enhancements upon binding to double-stranded DNA (see abstract and pages 2803-2804). Rye further teaches that the intercalators "allowed sensitive detection, quantitation, and accurate sizing of restriction fragments ranging from 600 to 24,000 bp (abstract)."

Regarding claims 13, 16, 17, 22, and 23, the fluorescent intercalators taught by Rye are backbone-specific labels that are detected with a fluorescence detection system (see pages 2803-2804 and pages 2807-2808).

Regarding claims 28-30, as evidenced by Thompson, the fluorescent intercalating dyes taught by Rye are photocleaving agents (see column 4, lines 3-25 and column 6, lines 1-31 of Thompson).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to detect bound oliognucleotide-nuclease P1 conjugates in the method of Fisher using the fluorescent intercalators taught by Rye. An ordinary artisan would have recognized that direct detection using the backbone-specific fluorescent intercalators of Rye would have been faster and simpler than the indirect method based on nuclease P1 activity taught by Fisher. Regarding claims 1, 91, and 126-130, use of the fluorescent intercalators taught by Rye in the method of Fisher would result in a detection method that is not dependent on the catalytic activity of nuclease P1. Further regarding claim 130, using the fluorescent intercalators would result in detection of the nucleic acid tag molecule rather than the nucleic acid binding enzyme. Regarding claims 16 and 17, use of the fluorescent intercalators taught by Rye in the method of Fisher would result in the nucleic acid polymer being labeled with a backbone-specific label. An

ordinary artisan would have had a reasonable expectation of success in using the fluorescent intercalator taught by Rye for detection of the bound oligonucleotide-nuclease P1 conjugates in the method of Fisher since both methods were directed to the same problem - detection of double-stranded DNA. Thus, the methods of claims 1, 2, 5-7, 9, 11-13, 16, 17, 22-31, 91, and 126-130 are prima facie obvious in view of the combined teachings of Fisher as evidenced by Chaudhry in view of Rye and Thompson.

9. Claims 19, 20, 33, and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fisher et al. (US 6,362,328 B1; cited previously) as evidenced by Chaudhry et al. (Nucleic Acids Research (1995) 23(19): 3805-3809; newly cited) in view of Kigawa et al. (US 5,965,361; cited previously) and further in view of Tegenfeldt et al. (WO 00/09757; cited previously).

These claims are drawn to the method of claim 1, wherein a single molecule linear polymer analysis system is used to determine a pattern of binding of the enzyme-nucleic acid conjugate to the nucleic acid polymer.

The combined teachings of Fisher, Chaudhry, and Kigawa result in the method of claims 1, 2, 5-7, 9, 11-15, 21-28, 30, 31, 91, and 126-130, as discussed above.

These references do not teach the use of a single molecule linear polymer analysis system to analyze the binding of the oligonucleotide-nuclease P1 conjugate to the nucleic acid polymer.

Tegenfeldt teaches a linear polymer analysis system for optically analyzing polymers (see abstract).

Regarding claim 19, the system is a linear polymer analysis system (abstract).

Regarding claim 20, Tegenfeldt teaches that the system is useful for performing a sequencing application wherein a nucleic acid is labeled with a fluorescent or radioactive label and subsequently exposed to an interaction station where the fluorescent/radioactive signal is detected (see pages 7-8, in particular the 1st full paragraph of page 8; see also claim 1).

Regarding claim 33, the system is capable of analyzing single polymers (page 8).

Regarding claim 34, the system described by Tegenfeldt is an optical mapping system (page 7, line 33 – page 8, line 4).

Tegenfeldt teaches the above method for the specific application of sequencing a nucleic acid molecule and also expression mapping, stating, "Since generation of expression maps involve the sequencing and identification of cDNA or mRNA, more rapid sequencing necessarily means more rapid generation of multiple expression maps (page 2, lines 3-5)."

Tegenfeldt also states, "The methods disclosed herein provide much longer read lengths than achieved by the prior art and a million-fold faster sequence reading (page 11, lines 13-14)."

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to use the detection system of Tegenfeldt to analyze the hybridization patterns produced by the method resulting from the combined teachings of Fisher, Chaudhry, and Kigawa. Tegenfeldt expressly taught that the disclosed linear analysis system possessed several advantages compared to conventional detection methods, namely increased assay speed and the ability to analyze longer nucleic acid fragments (see page 2, lines 3-5 and page 11, lines 13-14). Since the methods of Fisher and Kigawa were designed for mapping applications, an ordinary artisan would have been motivated by these teachings of Tegenfeldt to substitute single molecule linear polymer analysis for FISH in order to increase the speed and efficiency of the detection

step. An ordinary artisan would have also been motivated to utilize the linear polymer analysis method of Tegenfeldt, because its ability to detect single molecules (see page 8) would have increased the sensitivity of the method resulting from the combined teachings of Fisher, Chaudhry, and Kigawa. Since Tegenfeldt taught that the proposed read length is on the order of several hundred thousand nucleotides (see page 11), an ordinary artisan would have expected a reasonable level of success in analyzing the hybridization patterns generated by the method resulting from the combined teachings of Fisher, Chaudhry, and Kigawa using single molecule linear polymer analysis as taught by Tegenfeldt. Thus, the methods of claims 19, 20, 33, and 34 are prima facie obvious in view of the combined teachings of Fisher, Chaudhry, Kigawa, and Tegenfeldt.

10. Claim 32 is rejected under 35 U.S.C. 103(a) as being unpatentable over Fisher et al. (US 6,362,328 B1; cited previously) as evidenced by Chaudhry et al. (Nucleic Acids Research (1995) 23(19): 3805-3809; newly cited) in view of Kigawa et al. (US 5,965,361; cited previously) and further in view of Gite et al. (Journal of Molecular Recognition (1995) 8: 281-289; newly cited).

Claim 32 is drawn to the method of claim 31, wherein the nucleic acid binding enzyme is detected indirectly using an antibody or antibody fragment specific for the nucleic acid binding enzyme.

The combined teachings of Fisher, Chaudhry, and Kigawa result in the method of claims 1, 2, 5-7, 9, 11-15, 21-28, 30, 31, 91, and 126-130, as discussed above.

Regarding claim 32, Kigawa teaches detecting nucleic acid-RecA conjugates bound to a nucleic acid polymer by using an antibody specific to RecA (see column 6, lines 28-32 and

column 10, line 50 - column 11, line 28). Kigawa further states, "[B]y combining the foregoing detection methods and using a combination of RecA protein having a label or ligand, an anti-RecA antibody having a label or ligand, and a secondary antibody having a label or ligand that can be bound to the RecA antibody, it is possible to amplify a resultant signal to be much stronger than one attained by the conventional method (column 11, lines 22-28)."

However, Kigawa does not teach an antibody or antibody fragment specific to the S1 or P1 nucleases used in the conjugates of Fisher.

Gite teaches a method for purifying S1 nuclease using antibodies specific to the nuclease (see abstract and pages 282-283).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to indirectly detect the S1 nuclease in the oligonucleotide-enzyme conjugate of Fisher using an anti-S1 antibody since Kigawa taught that the use of antibody-based detection in combination with additional labels amplified the observed signal (column 11, lines 22-28). An ordinary artisan would have had a reasonable expectation of success in using anti-S1 antibody in the method, since Gite taught S1-specific antibodies (pages 282-283). Therefore, the method of claim 32 is prima facie obvious in view of the combined teachings of Fisher, Chaudhry, Kigawa, and Gite.

11. Claim 68 is rejected under 35 U.S.C. 103(a) as being unpatentable over Fisher et al. (US 6,362,328 B1; cited previously) in view of Kigawa et al. (US 5,965,361; cited previously) and further in view of Tegenfeldt et al. (WO 00/09757; cited previously).

Claim 68 is drawn to a method for analyzing a nucleic acid polymer comprising binding a covalently-linked conjugate comprising a nucleic acid tag molecule and a nucleic acid binding enzyme to a nucleic acid polymer and analyzing the binding using a linear polymer analysis system.

Regarding claim 68, Fisher teaches a method for analyzing a nucleic acid polymer comprising contacting a covalently-linked oligonucleotide-nuclease P1 conjugate with the nucleic acid polymer and analyzing the resulting hybridization pattern (see column 4, lines 37-64). In the method of Fisher, the nuclease binds to the nucleic acid polymer without cleavage (column 2, lines 48-62).

Fisher teaches detecting the binding of the oligonucleotide-nuclease conjugate to the nucleic acid polymer using a chemiluminescent assay that depends on the catalytic activity of the nuclease rather a method that does not depend on the catalytic activity of the nuclease. Fisher also does not teach analyzing the nucleic acid polymer using a linear polymer analysis system.

Kigawa teaches methods of analyzing nucleic acids using a conjugate comprising an oligonucleotide probe and RecA (see abstract and column 4, lines 7-31).

Regarding claim 68, the method of Kigawa comprises

(a) contacting the nucleic acid polymer with a conjugate comprising a nucleic acid tag molecule and a nucleic acid binding enzyme (see column 4, lines 7-25 or column 17, lines 5-25, where a conjugate comprising a biotinylated nucleic acid molecule (the "nucleic acid tag

molecule") and Cy3-labeled RecA (the nucleic acid binding enzyme) is added to a target nucleic acid; column 16, lines 5-45 teach preparation of the nucleic acid probe/Rec A conjugate)

(b) allowing the nucleic acid binding enzyme to bind to the nucleic acid polymer non-specifically and translocate along the polymer without cleavage of the polymer (column 2, lines 39-44 and column 17, lines 5-25)

(c) allowing the nucleic acid tag molecule to bind to the nucleic acid polymer in a sequence-specific manner, thereby labeling the nucleic acid polymer (see column 17, lines 5-25; see also column 4, lines 16-18 and column 6, lines 11-15)

(d) determining a pattern of binding of the conjugate to the nucleic acid polymer (column 17, lines 59-67; see also column 4, lines 27-31).

Kigawa teaches that the binding of the conjugate to the nucleic acid polymer is determined by measuring the fluorescence of a Cy3 label attached to the RecA protein or the signal of FITC derived from the biotinylated nucleic acid tag molecule (see column 17, lines 59-67). These methods do not rely on the catalytic activity of the nucleic acid binding enzyme.

Kigawa does not teach using a linear polymer analysis system to determine the hybridization pattern of the oligonucleotide-RecA conjugate to a target nucleic acid molecule.

Tegenfeldt teaches a linear polymer analysis system for optically analyzing polymers (see abstract). Tegenfeldt teaches that the system is useful for performing a sequencing application wherein a nucleic acid is labeled with a fluorescent or radioactive label and subsequently exposed to an interaction station where the fluorescent/radioactive signal is detected (see pages 7-8, in particular the 1st full paragraph of page 8; see also claim 1).

Regarding claim 68, Tegenfeldt teaches a method (see page 9, lines 6-15) comprising (a) generating optical radiation of a known wavelength to produce a localized radiation spot, (b) passing a polymer through a microchannel, (c) irradiating the polymer at the localized spot, (d) sequentially detecting radiation resulting from interaction of the polymer with the optical radiation at the localized radiation spot, and (e) analyzing the polymer based on the detected radiation.

Tegenfeldt teaches that the above method is useful for sequencing a nucleic acid molecule or expression mapping, stating, "Since generation of expression maps involve the sequencing and identification of cDNA or mRNA, more rapid sequencing necessarily means more rapid generation of multiple expression maps (page 2, lines 3-5)."

Tegenfeldt also states, "The methods disclosed herein provide much longer read lengths than achieved by the prior art and a million-fold faster sequence reading (page 11, lines 13-14)." It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Kigawa and Tegenfeldt to the method taught by Fisher. An ordinary artisan would have been motivated to label the nucleic acid tag molecule and/or the nucleic acid binding enzyme with detectable moieties, such as the fluorophores taught by Kigawa, recognizing that these labels permitted direct detection of the bound enzyme-oligonucleotide conjugate. An ordinary artisan would have been further motivated to detect the hybridization patterns resulting from the binding of the fluorescently labeled oligonucleotide-enzyme conjugate to the target nucleic acid using the linear polymer analysis system of Tegenfeldt since Tegenfeldt taught that this system offered several advantages compared to conventional detection methods, namely increased assay speed and the ability to analyze longer

nucleic acid fragments (see page 2, lines 3-5 and page 11, lines 13-14). Since the methods of Fisher and Kigawa were designed for mapping applications, an ordinary artisan would have been motivated by these teachings of Tegenfeldt to substitute single molecule linear polymer analysis for FISH in order to increase the speed and efficiency of the detection step. An ordinary artisan also would have been motivated to utilize the linear polymer analysis method of Tegenfeldt, because its ability to detect single molecules (see page 8) would have increased the sensitivity of the method. Since Tegenfeldt taught that the proposed read length is on the order of several hundred thousand nucleotides (see page 11), an ordinary artisan would have expected a reasonable level of success in analyzing the hybridization patterns generated by the method resulting from the combined teachings of Fisher and Kigawa using single molecule linear polymer analysis as taught by Tegenfeldt. An ordinary artisan also would have had a reasonable expectation of success in labeling the oligonucleotide-enzyme conjugate with a fluorophore for use in the linear polymer analysis system of Tegenfeldt, since methods for labeling proteins and nucleic acids with fluorescent labels were well known in the art as evidenced by the teachings of Kigawa (column 6, line 22 – column 7, line 60). Thus, the method of claim 68 is prima facie obvious in view of the combined teachings of Fisher and Tegenfeldt.

Response to Arguments

12. Applicant's arguments, see page 9, filed September 10, 2007, with respect to the rejection of claims 1, 2, 5-9, 11-17, 19-34, 68, 91, and 125-130 under 35 U.S.C. 112, 2nd paragraph, have been fully considered and are persuasive. Applicant's amendment overcomes the rejection, and therefore, it has been withdrawn.

Applicant's arguments, see pages 9-11, filed September 10, 2007, have been fully considered and were found persuasive with respect to the rejection of claims 1, 2, 5, 6, 11, 13-15, 21-27, 31, 32, 91, and 125-130 under 35 U.S.C. 102(b) as being anticipated by Kigawa and the rejection of claims 19, 20, 33, 34, and 68 under 35 U.S.C. 103(a) as being unptatentable over Kigawa in view of Tegenfeldt. Niether Kigawa nor the combination of Kigawa and Tegenfeldt teaches all of the elements of the amended claims, and therefore, the rejections have been withdrawn.

Applicant's arguments, see pages 10-11, filed September 10, 2007, with respect to the rejection of claims 1, 2, 5-9, 11-13, 16, 17, 22-25, 27-31, 91, and 126-130 under 35 U.S.C. 102(b) as being anticipated by Ecker, have been fully considered and are persuasive. This rejection has been withdrawn.

Conclusion

No claims are currently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela Bertagna whose telephone number is 571-272-8291. The examiner can normally be reached on M-F, 7:30 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Angela Bertagna
Art Unit 1637
November 21, 2007

amb AB

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER
11/26/07